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(54) Title: SUBSTITUTED NITROGEN-CONTAINING SIX-MEMBERED AMINO-HETEROCYCLES AS VANILLOID-1 RECEPTOR ANTAGONISTS FOR TREATING PAIN

(57) Abstract: The present invention provides a compound of formula(I): Y-J-NH-Z (I) wherein: Y is a quinoline or isoquinoline optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkoxy, nitro and amino; J is pyridine, pyridazine, pyrazine, pyrimidine or triazine optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkoxy, nitro and amino; wherein J is substituted at positions meta to each other by NH and Y; and Z is phenyl or pyridyl optionally substituted with one or two substituents independently elected from halogen, haloC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkoxy, nitro and amino; or a pharmaceutically acceptable salt thereof; pharmaceutical compositions containing the same; the compound for use in therapy; and use of the compound for the manufacture of a medicament for treating or preventing diseases requiring administration of an antagonist of the vanilloid-1 (VR1) receptor.

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SUBSTITUTED NITROGEN-CONTAINING SIX-MEMBERED AMINO-
HETEROCYCLES AS VANILLOID-1 RECEPTOR ANTAGONISTS FOR
TREATING PAIN

5 The present invention is concerned with substituted nitrogen-containing six-membered amino-heterocycles and analogues and derivatives thereof as well as pharmaceutically acceptable salts thereof, which are useful as therapeutic compounds, particularly in the treatment of pain and other conditions ameliorated by the modulation of the function of the vanilloid-1 receptor (VR1).

10 The pharmacologically active ingredient of chilli peppers has been recognised for some time to be the phenolic amide capsaicin. The application of capsaicin to mucous membranes or when injected intradermally, causes intense burning-like pain in humans. The beneficial effects of topical administration of capsaicin as an analgesic is also well established. However, understanding of the
15 underlying molecular pharmacology mediating these responses to capsaicin has been a more recent development.

 The receptor for capsaicin, termed the vanilloid VR1 receptor, was cloned by Caterina and colleagues at UCSF in 1997 (*Nature*, 398:816, 1997). VR1
20 receptors are cation channels that are found on sensory nerves that innervate the skin, viscera, peripheral tissues and spinal cord. Activation of VR1 elicits action potentials in sensory fibres that ultimately generate the sensation of pain. Importantly the VR1 receptor is activated not only by capsaicin but also by acidic pH and by noxious heat stimuli. It is also sensitized by a number of
25 inflammatory mediators and thus appears to be a polymodal integrator of painful stimuli.

 The prototypical VR1 antagonist is capsazepine (Walpole *et al.*, *J. Med. Chem.*, 37:1942, 1994) – VR1 IC₅₀ of 420nM. A novel series of sub-micromolar antagonists has also been reported recently (Lee *et al.*, *Bioorg. Med. Chem.*, 9:1713, 2001), but these reports provide no evidence for *in*
30 *vivo* efficacy. A much higher affinity antagonist has been derived from the 'ultra-potent' agonist resiniferatoxin. Iodo-resiniferatoxin (Wahl *et al.*, *Mol. Pharmacol.*, 59:9, 2001) is a nanomolar antagonist of VR1 but does not possess properties suitable for an oral pharmaceutical. This last is also true of the micromolar peptoid antagonists described by Garcia-Martinez (*Proc. Natl.*

Acad. Sci., USA, 99:2374, 2002). Most recently International (PCT) patent publication No. WO 02/08221 has described a novel series of VR1 antagonists, which are stated to show efficacy in a number of animal models. We herein describe another novel series of VR1 modulators. These comprise predominantly VR1 antagonists but encompass VR1 partial antagonists and VR1 partial agonists. Such compounds have been shown to be efficacious in animal models of pain.

Structurally related compounds are disclosed in WO-A-03099284 (Amgen Inc.) However there is no disclosure of the quinoline or isoquinoline moiety required by the present invention. Further, preferred compounds of the present invention have improved pharmacokinetics with lower clearance and thus improved half-life.

The present invention provides compounds of formula I:



(I)

wherein:

Y is a quinoline or isoquinoline optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

J is pyridine, pyridazine, pyrazine, pyrimidine or triazine optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₃₋₅cycloalkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

wherein J is substituted at positions *meta* to each other by NH and Y; and

Z is phenyl or pyridyl optionally substituted with one or two substituents independently selected from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

or a pharmaceutically acceptable salt thereof.

In one embodiment Y is a quinoline or isoquinoline optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

J is pyridazine, pyrazine, pyrimidine or triazine optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

wherein J is substituted at positions *meta* to each other by NH and Y;

Z is phenyl or pyridyl optionally substituted with one or two substituents independently selected from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

5 or a pharmaceutically acceptable salt thereof.

Preferred substituents include fluorine and methyl. Y is most preferably quinoline, particularly quinolin-7-yl. Y is particularly quinoline or isoquinoline.

Particular values of Y include quinolin-8-yl, quinoline-7-yl, 3-methylquinolin-7-yl, quinolin-5-yl, quinolin-6-yl, 6-fluoroquinolin-7-yl, 8-fluoroquinolin-7-yl, 6-trifluoromethylquinolin-7-yl, 8-fluoroquinolin-7-yl and isoquinolin-7-yl.

J can be unsubstituted, monosubstituted or disubstituted with substituents preferably chosen from chloro, fluoro, methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, methoxy, nitro and amino.

15 J is preferably unsubstituted or monosubstituted with fluorine, methoxy, methyl, amino or nitro. J is preferably pyrimidine, which may be substituted or unsubstituted. J may be pyridine, which may be substituted or unsubstituted.

Particular embodiments of J are pyrimidin-2-yl, pyrazin-2-yl, pyridazin-3-yl, pyrimidin-4-yl, pyridazin-4-yl, 1,3,5-triazin-2-yl, 5-methoxypyrimidin-4-yl, 5-methylpyrimidin-4-yl, 5-fluoropyrimidin-4-yl, 2-methoxypyrimidin-4-yl, 2-methylpyrimidin-4-yl, 5-nitropyrimidin-4-yl and 5-aminopyrimidin-4-yl. For the avoidance of doubt the preceding lists indicate the position of attachment to NH.

25 Z is preferably monosubstituted at a position *para* to the point of attachment to NH. Z may be substituted by F, CF₃ or OCF₃. The substituent is preferably CF₃. Thus Z may be 2-trifluoromethylpyrid-5-yl.

Particular embodiments of Z include 4-trifluoromethylphenyl, 3-trifluoromethylpyrid-6-yl and 2-trifluoromethylpyrid-5-yl. Further embodiments include 4-trifluoromethoxyphenyl and 2-fluoro-4-trifluoromethylphenyl.

Particularly preferred are compounds of formula I in which:

30 Y is a quinoline or isoquinoline optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

J is pyrimidine optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₃₋₅cycloalkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

wherein J is substituted at positions *meta* to each other by NH and Y; and

5 Z is pyridyl substituted at at least the position *para* to the point of attachment to NH by CF₃ or OCF₃ and which is optionally further substituted by halogen;

or a pharmaceutically acceptable salt thereof.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group
10 means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy. Examples of "C₃₋₇cycloalkyl" groups are cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl and methylcyclopropyl groups.

15 As used herein, the terms "haloC₁₋₆alkyl" and "haloC₁₋₆alkoxy" means a C₁₋₆alkyl or C₁₋₆alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by halogen atoms, especially fluorine or chlorine atoms. Preferred are fluoroC₁₋₆alkyl and fluoroC₁₋₆alkoxy groups, in particular, fluoroC₁₋₃alkyl and fluoroC₁₋₃alkoxy groups, for example, CF₃, CH₂CH₂F,
20 CH₂CHF₂, CH₂CF₃, OCF₃, OCH₂CH₂F, OCH₂CHF₂ or OCH₂CF₃, and most especially CF₃ and OCF₃.

When used herein, the term "halogen" or "halo" means fluorine, chlorine, bromine and iodine. The most preferred halogens are fluorine and chlorine, especially fluorine.

25 In a further aspect of the present invention, the compounds of formula I may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful
30 in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid

such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. A further salt is the acid addition salt with benzenesulfonic acid. Preferred pharmaceutically acceptable salts of the compounds of the present invention are the besylate salts. The hydrochloride salt can also be used. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the compound of formula I with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention also includes within its scope N-oxides of the compounds of formula I above. In general, such N-oxides may be formed on any available nitrogen atom. The N-oxides may be formed by conventional means, such as reacting the compound of formula I with oxone in the presence of wet alumina.

The present invention includes within its scope solvates of the compounds of formula I and salts thereof, for example, hydrates.

The compounds according to the invention may have one or more asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, the compounds of formula I may also exist in tautomeric forms and the invention includes within its scope both mixtures and separate individual tautomers.

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula I in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices, suppositories, creams or gels; for oral, parenteral, intrathecal, intranasal, sublingual, rectal or topical administration, or for administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers are particularly preferred. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. This solid pre-formulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Favoured unit dosage forms contain from 1 to 500 mg, for example 1, 5, 10, 25, 50, 100, 300 or 500 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions.

In the treatment of painful conditions such as those listed below, a suitable dosage level is about 1.0 mg to 15 g per day, preferably about 5.0 mg to 1 g per day, more preferably about 5 mg to 500 mg per day, especially 10 mg to

100 mg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

It will be appreciated that the amount of a compound of formula I required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

The invention further provides a compound of formula I as defined above, or a pharmaceutically acceptable salt thereof, for use in treatment of the human or animal body. Preferably, said treatment is for a condition which is susceptible to treatment by modulation (preferably antagonism) of VR1 receptors.

The compounds of the present invention will be of use in the prevention or treatment of diseases and conditions in which pain and/or inflammation predominates, including chronic and acute pain conditions. Such conditions include rheumatoid arthritis; osteoarthritis; post-surgical pain; musculo-skeletal pain, particularly after trauma; spinal pain; myofascial pain syndromes; headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain; ear pain; episiotomy pain; burns, and especially primary hyperalgesia associated therewith; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, pain associated with cystitis and labour pain, chronic pelvic pain, chronic prostatitis and endometriosis; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; itching conditions including pruritis, itch due to hemodialysis, and contact dermatitis; pain (as well as broncho-constriction and inflammation) due to exposure (e.g. via ingestion, inhalation, or eye contact) of mucous membranes to capsaicin and related irritants such as tear gas, hot peppers or pepper spray; neuropathic pain conditions such as diabetic neuropathy, chemotherapy-induced neuropathy and post-herpetic neuralgia; "non-painful" neuropathies; complex regional pain syndromes; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to

spinal cord or brain stem damage, low back pain, sciatica and ankylosing
spondylitis; gout; scar pain; irritable bowel syndrome; inflammatory bowel
disease; urinary incontinence including bladder detrusor hyper-reflexia and
bladder hypersensitivity; respiratory diseases including chronic obstructive
5 pulmonary disease (COPD), chronic bronchitis, cystic fibrosis, asthma and
rhinitis, including allergic rhinitis such as seasonal and perennial rhinitis, and
non-allergic rhinitis; autoimmune diseases; and immunodeficiency disorders. In
particular conditions that can be treated or prevented by the compounds of the
present invention include respiratory diseases such as chronic obstructive
10 pulmonary disease (COPD); chronic bronchitis; cystic fibrosis; asthma; and
rhinitis, including allergic rhinitis such as seasonal and perennial rhinitis, non-
allergic rhinitis and cough. The compounds of the present invention may also be
useful in the treatment of depression. They may also be used to treat gastro-
oesophageal reflux disease (GERD), particularly the pain associated with GERD.

15 Thus, according to a further aspect, the present invention provides a
compound of formula I for use in the manufacture of a medicament for the
treatment or prevention of physiological disorders that may be ameliorated by
modulating VR1 activity.

The present invention also provides a method for the treatment or
20 prevention of physiological disorders that may be ameliorated by modulating VR1
activity, which method comprises administration to a patient in need thereof of
an effective amount of a compound of formula I or a composition comprising a
compound of formula I.

According to a further or alternative aspect, the present invention
25 provides a compound of formula I for use in the manufacture of a medicament for
the treatment or prevention of a disease or condition in which pain and/or
inflammation predominates.

According to a further alternative aspect, the present invention provides a
compound of formula I for use in the manufacture of a medicament for the
30 treatment or prevention of respiratory diseases such as cough.

The present invention also provides a method for the treatment or
prevention of a disease or condition in which pain and/or inflammation
predominates, which method comprises administration to a patient in need

thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The present invention also provides a method for the treatment or prevention of respiratory diseases, such as cough, which method comprises
5 administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a compound according to the present invention and one or more other pharmacologically
10 active agents suitable for the treatment of the specific condition. The compound of formula I and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination.

Thus, for example, for the treatment or prevention of pain and/or inflammation, a compound of the present invention may be used in conjunction with other
15 analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, as well as opioid analgesics, especially morphine, NR2B antagonists, bradykinin antagonists, anti-migraine agents, anticonvulsants such as oxcarbazepine and carbamazepine, antidepressants (such as TCAs, SSRIs, SNRIs, substance P antagonists, etc.),
20 spinal blocks, gabapentin, pregabalin and asthma treatments (such as β_2 -adrenergic receptor agonists or leukotriene D₄ antagonists (e.g. montelukast).

Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, nabumetone, ketoprofen, naproxen, piroxicam and sulindac, etodolac, meloxicam, celecoxib, etoricoxib, parecoxib, valdecoxib and tilicoxib.
25 Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt
30 thereof. Suitable anti-migraine agents of use in conjunction with a compound of the present invention include CGRP antagonists, ergotamines or 5-HT₁ agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

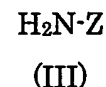
Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and

an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a disease or condition in which pain and/or inflammation predominates.

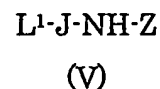
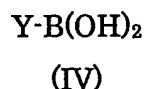
The compounds of formula I can be made by reacting a compound of formula II with a compound of formula III:

10



wherein J, Y and Z are as defined above and L^1 is a leaving group such as chlorine. The reaction can be carried out in the presence of a base such as sodium tertiarybutoxide or sodium hydrogencarbonate and a coupling agent such as 2'-(dimethylamino)-2-biphenyl palladium (II) chloride dinorbornylphosphine complex generally in a solvent such as toluene or tetrahydrofuran with heating to reflux for several hours to several days. Alternatively the reaction can be carried out in the presence of cesium carbonate, a coupling agent such as 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene and a catalyst such as $\text{Pd}_2(\text{dba})_3$, generally in a solvent such as anhydrous dioxane at reflux for several hours. The reaction can also be carried out in the presence of a base such as diisopropylethylamine in a solvent such as an anhydrous dimethylformamide between 0°C and room temperature for about 2 hours.

In an alternative process a compound of formula I can be made by reacting a compound of formula IV with a compound of formula V:



wherein J, L^1 , Y and Z are as defined above. The reaction can be carried out under conditions suitable for a Suzuki Coupling Reaction (for review, see for instance A. Suzuki, *Pure Appl. Chem.*, 1991, 63, 419-422), for example, in the

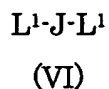
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presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium or dichloro-(1,4-bis(diphenylphosphino)butane)palladium, in a suitable solvent such as an ether, for example, dimethoxyethane or dioxane or an aromatic hydrocarbon, for example toluene, at an elevated temperature and in the presence of a base such as sodium carbonate or potassium phosphate.

The B(OH₂) moiety can be replaced by, for example, a 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl moiety. This group can be introduced by converting a methoxy group to a hydroxy group by refluxing with an acid catalyst such as aqueous hydrogen bromide for about five days, or boron tribromide in a solvent such as dichloromethane rising from 0°C to reflux and reacting for several hours. The hydroxy substituent is then reacted successively with trifluoromethanesulfonic acid anhydride in the presence of a base such as pyridine and a solvent such as dichloromethane at about room temperature for several hours; and then with bis(pinacolato)diboron and a base such as potassium acetate in a solvent such as 1,4-dioxane and a coupling agent such as Pd(dppf)Cl₂ at about 80°C for several hours.

When moiety Y is quinoline it can be made by reacting an aniline derivative with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in a solvent such as acetonitrile, followed by trimethyl orthoformate generally at reflux for about three hours. The product is heated in a high boiling solvent, such as Dowtherm A® for about one hour to obtain a quinolin-4(1H)-one. If a mixture of isomers is obtained these can be separated either before or after aromatising the quinoline which can be done by reacting with phosphorous oxychloride at about 80°C for about 1 hour.

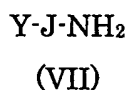
Compounds of formula II can be made by reacting a compound of formula IV with a compound of formula VI:



wherein J and L¹ are as defined above. The reaction is again a Suzuki Coupling Reaction. If necessary the compound of formula VI can be protected. For example when J is a pyridazine the starting chloropyridazinone can be protected with a tetrahydropyran group by heating with 3,4-dihydro-2H-pyran and an acid catalyst such as p-toluenesulfonic acid monohydrate at reflux for about 60 hours. After the Suzuki coupling the protecting group can be removed and the product chlorinated to produce the resulting compound of formula II using phosphorous oxychloride with heating to about 85°C.

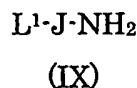
Compounds of formula V can be made by reacting a compound of formula III with a compound of formula VI under conditions as described for the reaction between compounds of formulae II and III above. The compound of formula VI may be protected as described above.

A further process for making compounds of formula I involves reacting a compound of formula VII with a compound of formula VIII:



wherein J, Y and Z are as defined above and L² is a leaving group such as bromine. The reaction conditions are as described above for the reaction between compounds of formulae II and III.

The compound of formula VII can be made by reacting a compound of formula IV with a compound of formula IX:

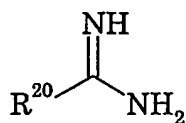


wherein L¹ and J are as defined above for a Suzuki Coupling Reaction.

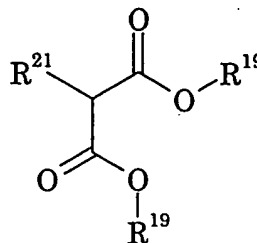
The NH₂ moiety in the compound of formula IX can be made by reacting a chlorine moiety with aqueous ammonia in a solvent such as butanol generally under pressure at about 90°C for about 2½ hours.

These compounds can be made by reacting compounds bearing two hydroxy moieties with phosphorous oxychloride generally in a solvent such as anhydrous toluene at about reflux in the presence of a base such as triethylamine for about one hour.

This compound when J is pyrimidine can be made by reacting a compound of formula X with a compound of formula XI:



(X)



(XI)

5

wherein R^{20} and R^{21} are optional substituents on J as defined above, and R^{19} are generally C_1 -alkyl groups. The reaction is carried out in a solvent such as ethanol generally for several hours in the presence of a strong base, such as sodium ethoxide. The amidine is usually introduced as the hydrochloride or acetate salt.

10

Compounds of formula I can be converted to other compounds of formula I by standard methods. For example, nitro groups can be converted to amino groups using a reducing agent such as 10% palladium on carbon under a hydrogen atmosphere generally in the presence of solvents such as methanol and dichloromethane for about two hours. Indeed such reactions can be carried out on any of the starting materials to introduce desired substituents. For example a methoxy group can be introduced on moiety J by displacing a chlorine using sodium methoxide and methanol at reflux for about two hours. A chlorine moiety can be removed by a reducing agent such as 10% palladium on carbon under a hydrogen atmosphere in the presence of a base such as triethylamine and a solvent such as methanol for several hours.

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A carboxy group can be converted to an amino group by reacting with diphenylphosphoryl azide in the presence of a base such as triethylamine in a solvent such as toluene. A Curtius rearrangement of the resulting azide, by heating in a solvent such as toluene at reflux for about one hour, following by reacting with 2-methyl-2-propanol for about five hours in a solvent such as toluene and then deprotecting with an acid such as trifluoroacetic acid in a solvent such as dichloromethane yields the desired amine.

Where the synthesis of intermediates and starting materials is not described these compounds are commercially available or can be made from commercially available compounds by standard methods.

During any of the above synthetic sequences it may be necessary and/or
5 desirable to protect sensitive or reactive groups on any of the molecules concerned.

The following Examples serve to illustrate the preparation of compounds of the present invention.

Description 1 2-Chloro-4-(quinolin-8-yl)pyrimidine

10 Pd(PPh₃)₄ (334 mg, 0.29 mmol) was added to a mixture of 2,4-dichloropyrimidine (861 mg, 5.78 mmol), quinoline-8-boronic acid (1.0 g, 5.78 mmol), and 2M aqueous sodium carbonate (2.89 ml, 5.78 mmol) in a mixture of toluene (50 ml) and ethanol (10 ml). The mixture was degassed three times and heated at reflux overnight. The reaction mixture was cooled and diluted with EtOAc (50 ml),
15 washed with water (2 x 100 ml), sat NaCl (100 ml), dried over Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography on silica: (eluent 2% MeOH in DCM + 0.5% NH₄OH) to give the title compound as a white solid (650 mg, 46%). ¹H NMR (500 MHz, CDCl₃) 7.49 (1 H, dd, *J* 8.3 and 4.2), 7.69 (1 H, t, *J* 7.9 and 7.6), 7.98 (1 H, d, *J* 8.1), 8.25 (1 H, dd, *J* 8.3 and 1.5), 8.43 (1 H, d, *J* 7.1), 8.46 (1 H, d, *J* 5.2), 8.69 (1 H, d, *J* 5.2), 8.97 (1 H, dd, *J* 3.9 and 1.5).
20

Description 2 2-Chloro-6-(quinolin-8-yl)pyrazine

Prepared from 2,6-dichloropyrazine according to the procedure of Description 1 to give a white solid (1.2 g, 86%). ¹H NMR (500 MHz, CDCl₃) 7.48 (1 H, dd, *J* 8.3
25 and 4.2), 7.69 (1 H, t, *J* 8.1 and 7.4), 7.95 (1 H, dd, *J* 8.1 and 1.2), 8.24 (1 H, dd, *J* 8.3 and 1.7), 8.27 (1 H, dd, *J* 7.1 and 1.5), 8.57 (1 H, s), 8.97 (1 H, dd, *J* 4.2 and 2.0), 9.52 (1 H, s).

Description 3 4-Chloro-6-(quinolin-8-yl)pyrimidine

30 To a mixture of 4,6-dichloropyrimidine (1.72 g, 11.6 mmol), quinoline-8-boronic acid (1.0 g, 5.78 mmol) and tripotassium phosphate (2.46 g, 11.6 mmol) in 1,4-dioxane (50 ml) was added Pd(PPh₃)₄ (334 mg, 0.29 mmol). The mixture was degassed three times and heated at reflux overnight. The reaction mixture was cooled and diluted with EtOAc (50 ml), washed with water (2 x 100 ml), sat. NaCl

(100 ml), dried over Na_2SO_4 , filtered and evaporated. The residue was purified by column chromatography on silica: (eluent 2% MeOH in DCM + 0.5% NH_4OH) to give the title compound as a white solid (200 mg, 14%). ^1H NMR (500 MHz, CDCl_3) 7.50 (1 H, dd, J 8.1 and 4.2), 7.71 (1 H, t, J 7.8 and 7.6), 7.98 (1 H, dd, J 8.1 and 1.3), 8.26 (1 H, dd, J 8.4 and 1.8), 8.41 (1 H, dd, J 7.3 and 1.5), 8.56 (1 H, d, J 1.0), 9.01 (1 H, dd, J 4.2 and 2.0), 9.12 (1 H, d, J 1.0).

Description 4 Quinolin-7-yl trifluoromethanesulfonate

To an ice-bath cooled suspension of 7-hydroxyquinoline (6.23 g, 42.9 mmol), and pyridine (4.51 ml, 55.77 mmol) in anhydrous dichloromethane (100 ml) was added dropwise trifluoromethanesulfonic anhydride (7.94 ml, 47.19 mmol) and the resulting mixture stirred at room temperature overnight. The mixture was washed with water (250 ml), sat. NaCl (150 ml), dried over Na_2SO_4 , filtered and evaporated to give the title compound as a beige solid (11.3 g, 95%). ^1H NMR (400 Hz, CDCl_3) 7.47-7.51 (2 H, m), 7.93 (1 H, d, J 9.0), 8.04 (1 H, d, J 2.4), 8.22 (1 H, dd, J 8.2 and 0.7), 9.00 (1 H, dd, J 4.3 and 1.9).

Description 5 7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline

To a mixture of Description 4 (8.7 g, 31.4 mmol), bis(pinacolato)diboron (8.8 g, 34.5 mmol), and potassium acetate (9.25 g, 94.2 mmol) in anhydrous 1,4-dioxane (150 ml) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (860 mg, 0.94 mmol). The mixture de-gassed three times and heated at 80°C overnight. The mixture was cooled and diluted with ethyl acetate (200 ml), washed with water (required a filtration through celite), sat. NaCl, dried over Na_2SO_4 , filtered and evaporated to give the title compound as a brown oil which solidified on standing. ^1H NMR (400 MHz, CDCl_3) 1.39 (12 H, s), 7.42 (1 H, dd, J 8.2 and 3.9), 7.79 (1 H, d, J 7.8), 7.90 (1 H, d, J 9.0), 8.15 (1 H, dd, J 8.6 and 1.2), 8.61 (1 H, s), 8.90 (1 H, dd, J 4.3 and 2.0).

Description 6 6-(Quinolin-7-yl)pyrimidin-4-amine

Prepared from 4-amino-6-chloropyrimidine (WO-A-0245652) and Description 5 according to the procedure of Description 1 to give a pale brown solid (600 mg, 38%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 7.01 (2 H, br s), 7.12 (1 H, d, J 1.0), 7.59 (1 H, dd, J 8.2 and 4.2), 8.10 (1 H, d, J 8.6), 8.21 (1 H, dd, J 8.6 and 1.6), 8.42 (1 H, dd, J 8.2 and 0.5), 8.53 (1 H, d, J 0.7), 8.62 (1 H, s), 8.98 (1 H, d, J 1.6).

Description 7 4-Amino-6-chloro-5-methoxypyrimidine

A mixture of 4,6-dichloro-5-methoxypyrimidine (5.0 g, 27.9 mmol), 33% aqueous ammonia (30 ml) and 1-butanol (15 ml) was heated at 90°C in a sealed tube for
5 2.5 hours. The mixture was allowed to cool and the precipitate removed by filtration, and dried to give the title compound as a white solid (1.8 g, 40%). ¹H NMR (400 MHz, DMSO-*d*₆) 3.71 (3 H, s), 7.30 (2 H, br s), 7.96 (1 H, s).

Description 8 4-Amino-6-chloro-5-methylpyrimidine

10 Prepared from 4,6-dichloro-5-methylpyrimidine according to the procedure of Description 7 to give a white solid (3.1 g, 70%). ¹H NMR (400 MHz, DMSO-*d*₆) 2.08 (3 H, s), 7.11 (2 H, br s), 8.06 (1 H, s).

Description 9 5-Methyl-6-(quinolin-7-yl)pyrimidin-4-amine

15 Prepared from Description 8 and Description 5 according to the procedure of Description 1 to give a beige solid (410 mg, 29%). ¹H NMR (400 MHz, CDCl₃) 2.22 (3 H, s), 5.09 (2 H, br s), 7.46 (1 H, dd, *J* 8.2 and 4.2), 7.79 (1 H, dd, *J* 8.4 and 1.5), 7.94 (1 H, d, *J* 8.4), 8.20-8.24 (2 H, m), 8.59 (1 H, s), 8.98 (1 H, d, *J* 1.5).

20 Description 10 4-Amino-6-chloro-5-fluoropyrimidine

Prepared from 4,6-dichloro-5-fluoropyrimidine (DE-A-10014607) according to the procedure of Description 7 to give a white solid (5.8 g, 94%). ¹H NMR (400 MHz, DMSO-*d*₆) 7.69 (2 H, br s), 8.07 (1 H, s).

25 Description 11 5-Fluoro-6-(quinolin-7-yl)pyrimidin-4-amine

Prepared from Description 10 and Description 5 according to the procedure of Description 1 to give a beige solid (900 mg, 64%). ¹H NMR (400 MHz, DMSO-*d*₆) 7.47 (2 H, br s), 7.63 (1 H, dd, *J* 8.2 and 4.2), 8.13 (1 H, d, *J* 8.6), 8.19 (1 H, d, *J* 8.6), 8.34 (1 H, d, *J* 2.3), 8.45 (1 H, d, *J* 8.1), 8.59 (1 H, s), 9.00 (1 H, d, *J* 1.4).

30

Description 12 4-Amino-6-chloro-2-methoxypyrimidine

Sodium methoxide (12 ml of a 25% wt solution in methanol) was added to methanol (300 ml) and to this mixture added 4-amino-2,6-dichloropyrimidine (5.00 g, 30.5 mmol). The resultant solution was heated at reflux for 2 hours and

then evaporated to dryness. The residue was treated with water (250 ml) and the precipitate which formed filtered and dried in vacuo to give the title product as a white solid (3 g, 61%). ¹H NMR (400 MHz, CDCl₃) 3.92 (3 H, s), 5.21 (2 H, br s), 6.14 (1 H, s).

5

Description 13 2-Methoxy-6-(quinolin-7-yl)pyrimidin-4-amine

Prepared from Description 12 and Description 5 according to the procedure of Description 1 to give an orange solid (1.15 mg, 65%). ¹H NMR (400 MHz, DMSO-*d*₆) 3.93 (3 H, s), 6.83 (1 H, s), 7.05 (2 H, br s), 7.59 (1 H, dd, *J* 8.3 and 4.2), 8.09 (1 H, d, *J* 8.6), 8.20 (1 H, dd, *J* 8.6 and 1.7), 8.42 (1 H, d, *J* 8.3), 8.63 (1 H, s), 8.98 (1 H, d, *J* 1.6).

Description 14 7-Methoxy-3-methylquinoline

To a nitrogen flushed suspension of 2-chloro-7-methoxy-3-methylquinoline [Organic Preparations and Procedures International (1990), 22(5), 579-88] (7.20 g, 34.7 mmol) and triethylamine (5.32 ml, 38.17 mmol) in methanol was added a spatula end of 10% Palladium on carbon and the resulting mixture stirred under a balloon of hydrogen overnight. The catalyst was removed by filtration and the filtrate evaporated. The residue was dissolved in dichloromethane (100 ml) and washed with water (150 ml), dried over Na₂SO₄, filtered and evaporated to give the title compound as a pale brown oil (6 g, 99%). ¹H NMR (400 MHz, CDCl₃) 2.47 (3 H, s), 3.94 (3 H, s), 7.16 (1 H, dd, *J* 8.9 and 2.5), 7.39 (1 H, d, *J* 2.5), 7.61 (1 H, d, *J* 8.9), 7.82 (1 H, t, *J* 0.9), 8.68 (1 H, d, *J* 2.2).

Description 15 3-Methylquinolin-7-ol

A mixture of Description 14 (6.0 g, 34.6 mmol) and 48% aqueous HBr (150 ml) was heated at reflux for 5 days. The mixture was cooled and basified by the careful addition of 33% aqueous ammonia. The resulting precipitate was removed by filtration, washed with water, and dried in vacuo to give the title compound as a pink solid (4.6 g, 84%). ¹H NMR (400 MHz, DMSO-*d*₆) 2.41 (3 H, s), 7.13 (1 H, dd, *J* 8.8 and 2.4), 7.22 (1 H, d, *J* 2.4), 7.71 (1 H, d, *J* 8.8), 7.96 (1 H, t, *J* 0.7), 8.61 (1 H, d, *J* 2.2), 10.01 (1 H, s).

Description 16 6-Chloro-5-nitro-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

To a suspension of 4,6-dichloro-5-nitropyrimidine (5.00 g, 25.8 mmol) in anhydrous tetrahydrofuran (100 ml) was added sodium hydrogen carbonate (2.38 g, 28.38 mmol) and 4-(trifluoromethyl)aniline (3.24 ml, 25.8 mmol), and the
5 resulting mixture stirred at room temperature for 3 days. The mixture was filtered and the filtrate evaporated. The residue triturated with diethyl ether and filtrate from trituration evaporated to give the title compound as a yellow solid (3.2 g, 38%). ¹H NMR (400 MHz, CDCl₃) 7.70 (4 H, q, *J* 9.0), 8.55 (1 H, s), 8.92 (1 H, s), 9.25 (1 H, br s).

10

Description 17 4-Chloro-6-(quinolin-5-yl)pyrimidine

Prepared from 4,6-dichloropyrimidine and quinoline-5-boronic acid according to the procedure of Description 1 to give a white solid. ¹H NMR (400 MHz, CDCl₃) 7.49 (1 H, dd, *J* 8.6 and 4.2), 7.69 (1 H, d, *J* 1.1), 7.76 (1 H, dd, *J* 7.2 and 1.3), 7.83
15 (1 H, dd, *J* 8.3 and 7.2), 8.28 (1 H, dd, *J* 7.4 and 1.0), 8.65 (1 H, dd, *J* 7.2 and 0.8), 8.65 (1 H, dd, *J* 4.2 and 1.9), 9.17 (1 H, d, *J* 1.0).

Description 18 5-[[4-(4-Fluoro-3-methoxyphenyl)amino]methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione

20 To a stirred solution of 4-fluoro-3-methoxyaniline (20 g, 142 mmol) in acetonitrile (200 ml) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (22.5 g, 156 mmol) followed by trimethyl orthoformate (18.6 ml, 170 mmol). The mixture was heated to reflux for 3 hours. The cooled mixture was filtered to give the title compound (30.9 g, 74%). ¹H NMR (400 MHz, CDCl₃) 1.76 (6 H, s), 3.94 (3 H, s),
25 6.76-6.83 (2 H, m), 7.14 (1 H, dd, *J* 10.5 and 8.4), 8.56 (1 H, d, *J* 14.4), 11.23 (1 H, d, *J* 14.4).

Description 19 6-Fluoro-7-methoxyquinolin-4(1*H*)-one

To a boiling solution of Dowtherm A® (80 ml) was added in portions Description
30 18 (30.9 g, 105 mmol). Heating was continued for 1 hour after the addition was complete and then the mixture cooled to room temperature. The mixture was poured into hexane (200 ml) and filtered. The filtrate was washed with more hexane to give a mixture of the title compound and 6-fluoro-5-methoxyquinolin-4(1*H*)-one in a 2:1 ratio (22.6 g, 100%).

Description 20 4-Chloro-6-fluoro-7-methoxyquinoline

A suspension of the crude product of Description 19 (22.6 g, 117mmol) in phosphorous oxychloride (110 ml, 1.18 mol) was heated at 80°C for 1 hour. The reaction mixture was allowed to cool and evaporated. The residue was neutralised with saturated sodium bicarbonate solution, extracted with DCM (3 x 200 ml) and evaporated. The residue was purified by column chromatography on silica (eluent 2% MeOH in DCM) to give the title compound (11 g, 44%). ¹H NMR (400 MHz, CDCl₃) 4.05 (3 H, s), 7.40 (1 H, dd, *J* 4.7 and 0.8), 7.53 (1 H, d, *J* 8.2), 7.85 (1 H, d, *J* 11.7), 8.68 (1 H, dd, *J* 4.7 and 0.8).

Description 21 6-Fluoro-7-methoxyquinoline

Prepared from Description 36 according to the procedure of Description 14. ¹H NMR (400 MHz, CDCl₃) 4.04 (3 H, s), 7.29-7.33 (1 H, m), 7.43 (1 H, d, *J* 11.3), 7.52 (1 H, d, *J* 8.2), 8.05 (1 H, dd, *J* 8.2 and 1.6), 8.82 (1 H, dd, *J* 4.3 and 1.2).

Description 22 6-Fluoroquinolin-7-ol

Prepared from Description 21 according to the procedure of Description 15 to give an off white solid (5.1 g, 60%). ¹H NMR (400 MHz, DMSO-*d*₆) 7.37-7.41 (1 H, m), 7.44 (1 H, d, *J* 8.4), 7.78 (1 H, d, *J* 11.9), 8.29 (1 H, dd, *J* 8.2 and 1.4), 8.78 (1 H, dd, *J* 4.4 and 1.4), 10.80-11.04 (1 H, br s).

Description 23 6-(6-Fluoroquinolin-7-yl)pyrimidin-4-amine

Prepared from Description 22 according to the procedures of Descriptions 4, 5 and 6 respectively. ¹H NMR (400 MHz, DMSO-*d*₆) 7.01 (1 H, s), 7.10 (2 H, s), 7.63 (1 H, m), 7.94 (1 H, d, *J* 12.1), 8.40 (1 H, d, *J* 8.2), 8.53 (1 H, d, *J* 1.2), 8.63 (1 H, d, *J* 7.4), 8.96 (1 H, dd, *J* 4.1 and 1.8).

Description 24 2-Fluoro-3-methoxyaniline

To a solution of 2-fluoro-3-methoxy benzoic acid [Synlett (1991), (10), 731-2] (15.0 g, 88 mmol) and triethylamine (13.49 ml, 96.8 mmol) in toluene (300 ml) was added diphenylphosphoryl azide (20.9 ml, 96.8 mmol) and the resulting mixture heated at reflux for 1 hour. After this time 2-methyl-2-propanol (12.5 ml, 132 mmol) was added and heating continued for 5 hours. The mixture was cooled and

evaporated, and the residue partitioned between water and dichloromethane. The dichloromethane layer was dried over Na₂SO₄, filtered through a 1 inch plug of silica and evaporated. The residue was dissolved in dichloromethane (200 ml) and trifluoroacetic acid (25 ml) added, and the resulting mixture stirred at room
5 temperature overnight. The mixture was evaporated and the residue partitioned between dichloromethane and sat. K₂CO₃, the dichloromethane layer was dried over Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography on silica: (eluent with 15% EtOAc in isohexanes) to give the title
10 compound as a pale yellow oil (10.8 g, 87%). ¹H NMR (400 MHz, CDCl₃) 3.72 (2 H, br s), 3.85 (3 H, s), 6.34-6.41 (2 H, m), 6.81-6.86 (1 H, m).

Description 25 8-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline

Prepared from 3-methoxy-2-methylaniline according to the procedures of Descriptions 18, 19, 20, 14, 15, 4 and 5 respectively to give an orange oil. ¹H NMR
15 (400 MHz, CDCl₃) 1.40 (12 H, s), 3.08 (3 H, s), 7.40 (1 H, dd, *J* 8.2 and 3.9), 7.62 (1 H, d, *J* 8.2), 7.85 (1 H, d, *J* 8.2), 8.10 (1 H, dd, *J* 8.2 and 2.0), 8.96 (1 H, dd, *J* 4.3 and 2.0).

Description 26 5-Fluoro-6-(8-methylquinolin-7-yl)pyrimidin-4-amine

20 Prepared from Description 10 and Description 25 according to the procedure of Description 1 to give a white solid (300 mg, 26%). ¹H NMR (400 MHz, CDCl₃) 2.77 (3 H, d, *J* 2.2), 5.26 (2 H, br s), 7.47 (1 H, dd, *J* 8.2 and 4.3), 7.56 (1 H, d, *J* 8.6), 7.77 (1 H, d, *J* 8.6), 8.18 (1 H, dd, *J* 8.2 and 2.0), 8.50 (1 H, d, *J* 2.4), 9.01 (1 H, dd, *J* 4.3 and 2.0).

25

Description 27 6-(8-Fluoroquinolin-7-yl)-5-methylpyrimidin-4-amine

Prepared from Description 24 according to the procedures of Descriptions 18, 19, 20, 14, 15, 4, 5 and 9 respectively. ¹H NMR (400 MHz, CDCl₃) 2.10 (3 H, d, *J* 3.3), 5.02 (2 H, s), 7.56-7.52 (1 H, m), 8.26-8.24 (1 H, m), 8.60 (1 H, s), 9.03 (1 H, dd, *J*
30 4.2 and 1.6).

Description 28 5-Methoxy-2-methylpyrimidine-4,6-diol

Sodium (7.00 g, 305.25 mmol), cut into small chunks, was added portionwise to anhydrous ethanol (300 ml). Once all the sodium had dissolved the mixture was

cooled in an ice-bath and acetamidine hydrochloride (9.57 g, 101.75 mmol) was added and the mixture stirred for 20 mins. To this mixture was added dropwise a solution of methoxy dimethylmalonate (15.0 g, 92.5 mmol) in ethanol (50 ml), and once addition was complete the mixture was stirred at room temperature overnight. The ethanol was removed by evaporation and the residue dissolved in water. The mixture was acidified by addition of conc. HCl and the resulting precipitate were removed by filtration and dried in vacuo to give the title compound (8 g, 55%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) 2.19 (3 H, s), 3.59 (3 H, s), 11.70 (2 H, brs).

Description 29 4,6-Dichloro-5-methoxy-2-methylpyrimidine

To a suspension of Description 28 (7.99 g, 51.2 mmol) and triethylamine (7.14 ml, 51.2 mmol) in anhydrous toluene (100 ml) heated at 100°C was added dropwise a solution of phosphorous oxychloride (10.5 ml, 112.6 mmol) in toluene (50 ml).

After complete addition the mixture was heated at reflux for 1 hour. The mixture was cooled in an ice bath and quenched by the careful addition of cold water (100 ml). The organic layer was washed with sat. NaHCO₃, sat. NaCl, and evaporated to dryness to give the title compound (9.5 g, 96%). ¹H NMR (400 MHz, CDCl₃) 2.65 (3 H, s), 3.95 (3 H, s).

Description 30 6-(6-Fluoroquinolin-7-yl)-5-methylpyrimidin-4-amine

Prepared from Description 22 and Description 8 according to the procedures of Descriptions 4, 5 and 6 respectively. ¹H NMR (400 MHz, DMSO-*d*₆) 1.90 (3 H, d, *J* 1.5), 5.75 (2 H, s), 7.62 (1 H, dd, *J* 8.4 and 4.0), 7.92 (1 H, d, *J* 10.4), 8.03 (1 H, d, *J* 7.0), 8.34 (1H, s) 8.43 (1 H, d, *J* = 8.4 Hz), 8.94 (1 H, dd, *J* 4.1 and 1.6).

Description 31 5,6-Dichloropyrimidin-4-amine

Prepared from diethyl chloromalonate and formamidine acetate according to the procedures of Descriptions 28, 29 and 7 respectively. ¹H NMR (400 MHz, DMSO-*d*₆) 7.46 (1 H, br s), 7.91 (1 H, br s), 8.17 (1 H, s).

Description 32 5-Chloro-6-quinolin-7-ylpyrimidin-4-amine

Prepared from Description 31 and Description 5 according to the procedure of Description 1 to give an off-white solid (1.1 g, 61%). ¹H NMR (500 MHz, DMSO-

*d*₆) 7.49 (2 H, br s), 7.62 (1 H, s), 7.90 (1 H, d, *J* 7.4), 8.10 (1 H, d, *J* 7.6), 8.35 (1 H, s), 8.45 (3 H, m), 8.98 (1 H, s).

Example 1 6-Quinolin-8-yl-N-[4-trifluoromethylphenyl]pyrazin-2-amine

5 To a mixture of Description 2 (200 mg, 0.83 mmol) and 4-trifluoromethylaniline (0.104 ml, 0.83 mmol) in anhydrous 1,4-dioxane (15 ml) was added cesium carbonate (379 mg, 1.16 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (29 mg, 0.05 mmol), and Pd₂(dba)₃ (15 mg, 0.017 mmol). The mixture was degassed three times and heated at reflux overnight. The mixture was cooled,
10 diluted with dichloromethane (10 ml), filtered through hyflo and the filtrate loaded directly onto a silica gel chromatography column: (eluent 2% MeOH in DCM + 0.5% NH₄OH). The product was further purified by mass-directed HPLC to give the title compound as a white solid (20 mg, 6.5%). ¹H NMR (500 MHz, CDCl₃) 6.92 (1 H, br s), 7.49 (1 H, dd, *J* 8.3 and 4.2), 7.56 (2 H, d, *J* 8.6), 7.68 (2 H, d, *J* 8.6), 7.71 (1 H, d, *J* 7.6), 7.95 (1 H, dd, *J* 8.3 and 1.3), 8.17 (1 H, dd, *J* 7.4 and 1.5), 8.25-8.27 (2 H, m), 8.95 (1 H, s), 9.00 (1 H, dd, *J* 4.2 and 1.7); *m/z* (ES⁺) 367 (M+H⁺).

The following compounds were made by the procedure of Example 1:

20

Example 2 6-Quinolin-8-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine

Prepared from Description 3 and 4-trifluoromethylaniline to give a white solid (6 mg, 4%). ¹H NMR (500 MHz, CDCl₃) 7.47 (1 H, dd, *J* 8.3 and 4.2), 7.56 (2 H, d, *J* 8.8), 7.62 (2 H, d, *J* 8.8), 7.71 (1 H, t, *J* 7.9 and 7.6), 7.78 (1 H, s), 7.82 (1 H, s),
25 7.94 (1 H, dd, *J* 8.3 and 1.3), 8.26 (1 H, dd, *J* 8.3 and 1.5), 8.32 (1 H, dd, *J* 7.4 and 1.3), 8.87 (1 H, s), 8.94 (1 H, dd, *J* 4.2 and 1.7); *m/z* (ES⁺) 367 (M+H⁺).

Example 3 6-Quinolin-7-yl-N-[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine

Prepared from Description 6 and 2-bromo-5-trifluoromethylpyridine to give a
30 white solid (100 mg, 60%). ¹H NMR (500 MHz, CDCl₃) 7.48 (1 H, dd, *J* 8.3 and 4.2), 7.73 (1 H, d, *J* 8.8), 7.79 (1 H, br s), 7.90 (1 H, dd, *J* 8.7 and 2.2), 7.97 (1 H, d, *J* 8.6), 8.23 (1 H, d, *J* 7.7), 8.31 (1 H, s), 8.36 (1 H, dd, *J* 8.5 and 1.7), 8.67 (1 H, s), 8.80 (1 H, s), 9.00 (1 H, s), 9.01 (1 H, d, *J* 1.7); *m/z* (ES⁺) 368 (M+H⁺).

Example 4 5-Fluoro-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine

Prepared from Description 11 and 4-trifluoromethylbromobenzene to give a white solid (194 mg, 61%). ¹H NMR (400 MHz, CDCl₃) 7.27 (1 H, d, *J* 3.1), 7.49 (1 H, dd, *J* 8.2 and 4.3), 7.66 (2 H, d, *J* 8.6), 7.90 (2 H, d, *J* 8.6), 7.98 (1 H, d, *J* 8.6), 8.23 (1 H, d, *J* 8.2), 8.29 (1 H, d, *J* 8.6), 8.70 (1 H, d, *J* 1.6), 8.83 (1 H, s), 9.00 (1 H, dd, *J* 4.3 and 1.6); *m/z* (ES⁺) 385 (M+H⁺).

Example 5 2-Methoxy-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine

Prepared from Description 13 and 4-trifluoromethylbromobenzene to give an off white solid (130 mg, 41%). ¹H NMR (400 MHz, CDCl₃) 4.11 (3 H, s), 7.00 (1 H, s), 7.38 (1 H, br s), 7.45 (1 H, dd, *J* 8.2 and 4.3), 7.64 (4 H, s), 7.90 (1 H, d, *J* 8.6), 8.19 (1 H, d, *J* 7.4), 8.27 (1 H, dd, *J* 8.6 and 1.6), 8.69 (1 H, s), 8.96 (1 H, dd, *J* 4.3 and 2.0); *m/z* (ES⁺) 397 (M+H⁺).

Example 6 6-Quinolin-5-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine

Prepared from Description 17 and 4-trifluoromethylaniline to give a white solid. ¹H NMR (400 MHz DMSO-*d*₆) 7.16 (1 H, d, *J* 1.2), 7.59 (1 H, dd, *J* 4.2 and 8.8), 7.72 (2 H, d, *J* 8.8), 7.83 (1 H, dd, *J* 7.1 and 1.2), 7.88-7.91 (1 H, m), 8.01 (2 H, d, *J* 8.6), 8.17 (1 H, d, *J* 8.3), 8.69 (1 H, d, *J* 8.6), 8.90 (1 H, d, *J* 1.2), 8.98 (1 H, dd, *J* 3.9 and 1.7), 10.20 (1 H, s); *m/z* (ES⁺) 367 (M+H⁺).

Example 7 6-(6-Fluoroquinolin-7-yl)-N-[4-trifluoromethylphenyl]pyrimidin-4-amine

Prepared from Description 23 and 4-trifluoromethylbromobenzene to give a white solid (28 mg, 43%). ¹H NMR (400 MHz, DMSO-*d*₆) 7.49 (1 H, s), 7.63-7.67 (1 H, m), 7.72 (2 H, d, *J* 8.4), 8.01 (3 H, m), 8.44 (1 H, dd, *J* 8.4 and 1.1), 8.75 (1 H, d, *J* 7.4), 8.91 (1 H, d, *J* 1.1), 8.99 (1 H, dd, *J* 4.2 and 1.8), 10.25 (1 H, s); *m/z* (ES⁺) 385 (M+H⁺).

Example 8 5-Nitro-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine

To a mixture of Description 16 (2.01 g, 6.3 mmol) and Description 5 (2.41 g, 9.45 mmol) in a mixture of toluene (50 ml) and ethanol (10 ml) was added 2M sodium carbonate (3.15 ml, 6.3 mmol) and Pd(PPh₃)₄ (364 mg, 0.315 mmol). The mixture was de-gassed three times and heated at reflux overnight. The cooled mixture was diluted with EtOAc (100 ml) and washed with water (200 ml), sat. NaCl (100 ml), dried over Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography on silica: (eluent 1% MeOH in DCM +0.5% NH₃) then a second column (eluent 20% EtOAc in iso-hexanes). The product triturated with diethyl ether to give the title compound as a pale yellow solid (100 mg, 4%). ¹H NMR (500 MHz, CDCl₃) 7.50 (1 H, dd, *J* 8.3 and 4.2), 7.70 (2 H, d, *J* 8.1), 7.72 (1 H, dd, *J* 8.6 and 1.7), 7.81 (2 H, d, *J* 8.1), 7.95 (1 H, d, *J* 8.6), 8.24 (1 H, d, *J* 7.6), 8.36 (1 H, s), 8.87 (1 H, s), 9.00 (1 H, dd, *J* 4.2 and 1.7); *m/z* (ES⁺) 412 (M+H⁺).

Examples 9-13 were made from the indicated compounds according to the procedure of Example 2.

Example 9 6-(8-Fluoroquinolin-7-yl)-5-methyl-N-[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine

Description 27 and 2-bromo-5-trifluoromethylpyridine gave a solid (171 mg, 72%). ¹H NMR (400 MHz, DMSO-*d*₆) 2.23 (3 H, d, *J* 2.2), 7.68 (1 H, dd, *J* 8.4 and 6.5), 7.73 (1 H, dd, *J* 8.4 and 4.2), 7.97 (1 H, d, *J* 8.5), 8.19 (1 H, dd, *J* 9.0 and 2.4), 8.39 (1 H, d, *J* 8.8), 8.54 (1 H, d, *J* 8.4), 8.73 (1 H, s), 8.81 (1 H, s), 9.04 (1 H, dd, *J* 4.2 and 1.6), 9.66 (1 H, s); *m/z* (ES⁺) 400 (M+H⁺).

Example 10 5-Methyl-6-quinolin-7-yl-N-[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine

Description 9 and 2-bromo-5-trifluoromethylpyridine gave a white solid (180 mg, 55%). ¹H NMR (500 MHz, CDCl₃) 2.43 (3 H, s), 7.48 (1 H, dd, *J* 8.3 and 4.2), 7.66 (1 H, s), 7.80 (1 H, dd, *J* 8.4 and 1.5), 7.97 (2 H, d, *J* 8.5), 8.23 (2H, m), 8.56 (1 H, s), 8.80 (1 H, d, *J* 8.8), 8.87 (1 H, s), 9.00 (1 H, dd, *J* 4.2 and 1.5); *m/z* (ES⁺) 382 (M+H⁺).

Example 11 6-(6-Fluoroquinolin-7-yl)-5-methyl-N[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine

Description 30 and 2-bromo-5-trifluoromethylpyridine gave a solid (5 mg, 3%). ¹H NMR (500 MHz, DMSO-*d*₆) 2.22 (3 H, s), 7.66 (1 H, dd, *J* 8.4 and 4.2), 7.99 (1 H, d, *J* 10.3), 8.13 (1 H, d, *J* 7.0), 8.19 (1 H, d, *J* 8.9), 8.38 (1 H, d, *J* 8.9), 8.46 (1 H, d, *J* 8.2), 8.73 (1 H, s), 8.80 (1 H, s), 8.97 (1 H, d, *J* 2.8), 8.97 (1 H, d, *J* 2.8), 9.66 (1 H, s); *m/z* (ES⁺) 400 (M+H⁺).

Example 12 5-Fluoro-6-(8-methylquinolin-7-yl)-N[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine

Description 26 and 2-bromo-5-trifluoromethylpyridine gave a white solid (40 mg, 41%). ¹H NMR (500 MHz, CDCl₃) 2.80 (3 H, s), 7.26 (1 H, s), 7.49 (1 H, dd, *J* 8.3 and 4.2), 7.58 (1 H, *J* 8.6), 7.80 (1 H, d, *J* 8.6), 8.00 (1 H, *J* 8.6), 8.07 (1 H, s), 8.19 (1 H, *J* 7.6), 8.59 (1 H, s), 8.78 (2 H, t, *J* 4.5 and 3.9), 9.02 (1 H, d, *J* 2.7); *m/z* (ES⁺) 400 (M+H⁺).

Example 13 5-Chloro-6-quinolin-7-yl-N[4-trifluoromethylphenyl]pyrimidin-4-amine

Description 32 and 4-trifluoromethylbromobenzene gave a white solid (180 mg, 57%). ¹H NMR (400 MHz, DMSO-*d*₆) 7.65 (1 H, t, *J* 3.7), 7.74 (2 H, d, *J* 7.9), 7.94 (1 H, d, *J* 8.2), 8.01 (2 H, d, *J* 7.9), 8.13 (1 H, d, *J* 8.2), 8.41 (1 H, s), 8.47 (1 H, d, *J* 8.0), 8.72 (1 H, s), 9.01 (1 H, s), 9.58 (1 H, s); *m/z* (ES⁺) 401 (M+H⁺).

Example 14 7-(5-Methyl-6-[[5-trifluoromethylpyridin-2-yl]amino]pyrimidin-4-yl)quinolinium benzenesulfonate

To a solution of Example 10 in DMF (40 ml) was added benzenesulfonic acid (1.05 eq., 4.3 g, 27.2 mmol) at 40°C. Isopropyl acetate (10 ml) was added into the solution, which was then seeded with the product (10 mg). The solution was aged for 30 min, then more isopropyl acetate (70 ml) was added over 1~2 hours, keeping the internal temperature at ca. 40°C. After addition, the batch was cooled to 20-25°C, aged for 2 hours, then filtered. The resulting cake was washed with isopropyl acetate (10 mL), then dried to give the title compound (13.4 g, 95 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.07 (1H, br s), 9.26 (1H, dd, *J*=4.8, 1.5

Hz), 8.94 (1H, d, J= 8.2 Hz), 8.90 (1H, s), 8.79 (1H, m), 8.38 (1H, d, J=8.6 Hz), 8.36 (1H, m), 8.32 (1H, d, J=8.8 Hz), 8.25 (1H, dd, J=8.9, 2.4 Hz), 8.02 (1H, dd, J= 8.5, 1.6 Hz), 7.97 (1H, dd, J=8.4, 4.8 Hz), 7.64-7.58 (2 H, om), 7.35-7.26 (3H, om), 2.37 (3H, s); m/z (ES⁺) 382 (M+H⁺).

5

The following compounds can be prepared according to the procedure described in Example 14.

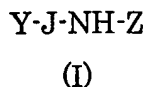
Example	Title
15	7-(2-Cyclopropyl-5-methyl-6-{{5-trifluoromethylpyridin-2-yl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate.
16	7-(2-Cyclopropyl-5-methyl-6-{{4-trifluoromethylphenyl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate.
17	7-(5-Isopropyl-6-{{5-trifluoromethylpyridin-2-yl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate.
18	6-Fluoro-7-(5-methyl-6-{{5-trifluoromethylpyridin-2-yl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate.
19	6-Fluoro-7-(5-methyl-6-{{4-trifluoromethylphenyl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate.
20	7-(5-Fluoro-6-{{5-trifluoromethylpyridin-2-yl}amino}pyrimidin-4-yl)-8-methylquinolinium benzenesulfonate.

10

CLAIMS

1. A compound of formula I:

5



wherein:

Y is a quinoline or isoquinoline optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

10

J is pyridine, pyridazine, pyrazine, pyrimidine or triazine optionally substituted with one or two substituents independently chosen from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₃₋₅cycloalkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino;

15

wherein J is substituted at positions *meta* to each other by NH and Y; and Z is phenyl or pyridyl optionally substituted with one or two substituents independently selected from halogen, haloC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, nitro and amino; or a pharmaceutically acceptable salt thereof.

20

2. A compound according to claim 1 wherein Y is quinoline or isoquinoline optionally substituted by fluorine or methyl.

3. A compound according to claim 1 or 2 wherein J is pyrimidine optionally substituted by fluorine, methoxy, methyl, amino or nitro.

25

4. A compound according to claim 1, 2 or 3 wherein Z is substituted at the position *para* to the point of attachment to NH with trifluoromethyl.

30

5. A compound which is:

4-quinolin-8-yl-N-[4-trifluoromethylphenyl]pyrimidin-2-amine;

6-quinolin-8-yl-N-[4-trifluoromethylphenyl]pyrazin-2-amine;

5-quinolin-8-yl-N-[4-trifluoromethylphenyl]pyridazin-3-amine;

6-quinolin-8-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;

- 6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrazin-2-amine;
 4-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-2-amine;
 6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyridazin-3-amine;
 5 6-quinolin-7-yl-N-[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 6-quinolin-7-yl-N-[6-trifluoromethylpyridin-3-yl]pyrimidin-4-amine;
 5-methoxy-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-methyl-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-fluoro-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 10 2-methoxy-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 2-methyl-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 6-(3-methylquinolin-7-yl)-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 6-quinolin-5-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 6-quinolin-6-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 15 6-(2-methylquinolin-7-yl)-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 6-(6-fluoroquinolin-7-yl)-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 6-(8-fluoroquinolin-7-yl)-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 N-[4-(trifluoromethyl)phenyl]-6-[6-trifluoromethylquinolin-7-yl]pyrimidin-4-amine;
 20 6-(8-methylquinolin-7-yl)-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-fluoro-6-(8-methylquinolin-7-yl)-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 6-isoquinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 6-quinolin-8-yl-N-[4-trifluoromethylphenyl]pyridazin-4-amine;
 4-quinolin-8-yl-N-[4-trifluoromethylphenyl]-1,3,5-triazin-2-amine;
 25 5-nitro-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 6-quinolin-7-yl-N⁴-[4-trifluoromethylphenyl]pyrimidine-4,5-diamine;
 and the pharmaceutically acceptable salts thereof.

6. A compound which is:

- 30 6-(8-fluoroquinolin-7-yl)-5-methyl-N-[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 6-(8-fluoroquinolin-7-yl)-5-methyl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-methoxy-2-methyl-6-quinolin-7-yl-N-[4-trifluoromethylphenyl]pyrimidin-4-amine;

- 2-methyl-6-(8-methylquinolin-7-yl)-*N*[4-trifluoromethylphenyl]pyrimidin-4-amine;
N[2-fluoro-4-trifluoromethylphenyl]-5-methoxy-6-quinolin-7-ylpyrimidin-4-amine;
 5 5-methoxy-6-quinolin-7-yl-*N*[4-trifluoromethoxyphenyl]pyrimidin-4-amine;
 5-methyl-6-(8-methylquinolin-7-yl)-*N*[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-methyl-6-(8-methylquinolin-7-yl)-*N*[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 10 6-quinolin-7-yl-5-trifluoromethyl-*N*[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-ethyl-6-quinolin-7-yl-*N*[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-ethyl-6-quinolin-7-yl-*N*[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 5-methyl-6-quinolin-7-yl-*N*[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 2-cyclopropyl-5-methyl-6-quinolin-7-yl-*N*[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 15 2-cyclopropyl-5-methyl-6-quinolin-7-yl-*N*[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-isopropyl-6-quinolin-7-yl-*N*[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 6-(6-fluoroquinolin-7-yl)-5-methyl-*N*[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 20 6-(6-fluoroquinolin-7-yl)-5-methyl-*N*[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-fluoro-6-(8-methylquinolin-7-yl)-*N*[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
N(2-quinolin-7-ylpyridin-4-yl)-5-trifluoromethylpyridin-2-amine;
 25 2-quinolin-7-yl-*N*[4-trifluoromethylphenyl]pyridin-4-amine;
 5-chloro-6-quinolin-7-yl-*N*[4-trifluoromethylphenyl]pyrimidin-4-amine;
 5-chloro-6-quinolin-7-yl-*N*[5-trifluoromethylpyridin-2-yl]pyrimidin-4-amine;
 and the pharmaceutically acceptable salts thereof.
- 30 7. A pharmaceutically acceptable salt which is:
 7-5-methyl-6-{{5-(trifluoromethyl)pyridin-2-yl}amino}pyrimidin-4-yl quinolinium benzenesulfonate;
 7-(2-cyclopropyl-5-methyl-6-{{5-(trifluoromethyl)pyridin-2-yl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate;

7-(2-cyclopropyl-5-methyl-6-{{4-(trifluoromethyl)phenyl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate;

7-(5-isopropyl-6-{{5-(trifluoromethyl)pyridin-2-yl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate;

5 6-fluoro-7-(5-methyl-6-{{5-(trifluoromethyl)pyridin-2-yl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate;

6-fluoro-7-(5-methyl-6-{{4-(trifluoromethyl)phenyl}amino}pyrimidin-4-yl)quinolinium benzenesulfonate.

10 8. A pharmaceutical composition comprising a compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof or a salt of claim 7 and a pharmaceutically acceptable carrier.

9. A compound of any one of claims 1 to 6 or a pharmaceutically acceptable
15 salt thereof or a salt of claim 7 for use in a method of treatment of the human or animal body by therapy.

10. Use of a compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof or a salt of claim 7 for the manufacture of a medicament
20 for treating pain, chronic obstructive pulmonary disease, depression or gastro-oesophageal reflux disease.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/004730

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 C07D401/14 A61K31/506 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/08221 A (NEUROGEN CORPORATION; HUTCHISON, ALAN; DESIMONE, ROBERT, W; HODGETTS,) 31 January 2002 (2002-01-31) cited in the application the whole document	1,7,8,10

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/004730

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